REMARKS

In the Final Action dated October 28, 2010, claims 1-5, 8, 9, 13-16, 19, 20, 22-25, 30-34, 37-39, and 41-55 were pending and under examination. Claims 16 and 33 were objected to for formal matters. Claims 13, 14, 16 and 50-55 were rejected under 35 U.S.C. §101 as allegedly directed to non-statutory matter. All claims were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher et al. (US 2002/0059652) ("Glimcher") in view of Shaffer et al. (*Immunity*, 2002, 17: 51-62) ("Shaffer"), Pol et al. (*J. Biomol. Screening* 2002, 7: 325-332) ("Pol"), and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307) ('Mountford").

This Response addresses the Examiner's rejection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

Claims 1-5, 8-9 and 48-49 are directed to a genetically modified non-human organism. Independent claim 1 has been amended to recite that the organism is capable of producing functional Blimp protein. Support for such amendment is found in the specification, e.g., page 6, lines 18-25. The term "capable of" is used to reflect that the Blimp protein is not constitutively produced and will be produced from either or both of the modified and unmodified *Blimp* alleles under the endogenous Blimp promoter in certain lineages of cells at certain differentiation stage. See, e.g., page 6, lines 1-5 of the specification.

Claims 50-55 and 13-16 are directed to a genetically modified cell. Independent claim 50 has been amended to define the cell as "isolated", and to recite that the cell is capable of producing functional Blimp protein.

Claim 20 and its dependent claims (claims 22, 24-25, and new claims 56-60) are

directed to a method of isolating antibody secreting cells. The previous version of claim 20 includes an initial step of providing a genetically modified cell or non-human organism. Claim 20 has been amended herein to clarify that the method is directed to isolating antibody secreting cells (ASCs) from a population of genetically modified cells, and in new dependent claims (claims 56-60), such genetically modified cells are delineated as derived from an embryonic cell (claim 56) or obtained from a genetically modified non-human organism (claims 57-60). Amended claim 20 finds support in the specification, e.g., page 8, lines 29-30. Claim 56 finds support in previous claim 39. Claims 57-60 find support in previous claim 38 and in the specification, e.g., page 65, lines 10-12.

New independent claim 61 is directed to a method for screening *in vitro* for agonist or antagonist of differentiation to antibody secreting cells, which finds support in previous claim 30. New claims 62-66 depend from claim 61, and further define the origin of the cells employed in the method of claim 61, i.e., derived from an embryonic cell (claim 62) or obtained from a genetically modified non-human organism (claims 63-66). Similarly, claims 62-66 are supported by previous claims 38-39, and the specification, e.g., page 65, lines 10-12.

New independent claim 67 is directed to a method for screening *in vivo* for agonist or antagonist of differentiation to antibody secreting cells, which finds support in previous claim 30. New claim 68 depends from claim 67, and further defines the non-human organism to be a laboratory test animal.

New claims 69-72 depend from claims 20, 61 and 67, and further define the modified *Blimp* allele, as supported by the specification and other claims, e.g., claims 2-5.

Claims 23, 30-34, 37-39 and 41-47 have been canceled without prejudice or disclaimer.

The foregoing amendments are fully supported by the application as originally filed and do not introduce new matter. Therefore, entry of these amendments is warranted. Following entry of the amendments, claims 1-5, 8-9, 13-16, 19-20, 22, 24-25 and 48-72 will be pending and under examination.

Claim Objections

The Examiner objected to the language "the T-cells are selected from $CD4^+$ T-cells *or* $CD8^+$ T-cells" recited in claim 16 and required appropriate correction. The Examiner also objected to the language "[t]he cell or non-human organism of claim 31" recited in claim 33 and required appropriate correction.

Applicants have herein amended claim 16 to recite the language "the T-cells are selected from $CD4^+$ T-cells and $CD8^+$ T-cells," as suggested by the Examiner. Applicants have also canceled claim 33, thereby rendering the objection thereto moot. Accordingly, Applicants respectfully request that the Examiner withdraw the objections to claims 16 and 33.

Claim Rejection Under 35 U.S.C. § 101

The Examiner rejected claims 50-55, 13, 14, and 16 under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner asserted that claims 50-55, 13, 14, and 16 encompass cells existent in a human being and that human beings are non-statutory subject matter.

Applicants have herein amended independent claim 50 to recite "isolated" cell. Withdrawal of the rejection is therefore respectfully requested.

Claim Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected all of the claims under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher et al. (US 2002/0059652) ("Glimcher") in view of Shaffer et al. (*Immunity*, 2002, 17: 51-62) ("Shaffer"), Pol et al. (*J. Biomol. Screening* 2002, 7: 325-332) ("Pol"), and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307) ('Mountford").

Applicants previously submitted that those skilled in the art would not have been motivated to rely on the teachings of Glimcher directed to XBP-1, and substitute XBP-1 with Blimp, because those skilled in the art would not have considered Blimp and XBP-1 as equivalent markers. Applicants also submitted that even if one were to attempt, an XBP-1 based reporter system would not work to uniquely identify ASCs because of the ubiquitous expression pattern of XBP-1.

The Examiner did not consider these arguments to be persuasive, allegedly because Glimcher already teaches XBP-1 transgenic mice, wherein the mice are used to identify agonists or antagonists of ASCs differentiation.

Applicants also submitted previously that because neither the expression of XBP-1 nor Blimp-1 was limited to a particular cell-type, those skilled in the art would not have been motivated to make a Blimp transgenic animal in order to specifically identify and isolate all ASCs, or at least very least, would not have reasonably expected the successful results achieved by the invention.

The Examiner responded by stating that the argument of unexpected results are not found persuasive because none of the claims are drawn to a method of isolating ASCs by using a transgenic animal.

Applicants respectfully submit that the claims as presented herein are unobvious over

the cited combination of art, and favorable consideration is respectfully requested.

Specifically, claim 20 and its dependent claims (claims 22, 24-25, 56-60, and 69-72) are presently directed to methods of isolating ASCs from a population of genetically modified cells. Dependent claims 57-60 further define the population of cells as obtained from a genetically modified organism. With respect to these claims, Applicants respectfully submit that the art of record simply does not provide the recognition that the expression from the *Blimp* gene, as indicated by a reporter molecule, coincides with the commitment of cells to differentiate to ASCs or the identity of ASCs themselves. Applicants reassert that those skilled in the art would not have been motivated to rely on the teachings of Glimcher directed to XBP-1, and substitute XBP-1 with Blimp, because those skilled in the art would not have considered Blimp and XBP-1 as equivalent markers. Furthermore, because neither the expression of XBP-1 nor Blimp-1 was limited to a particular cell-type, those skilled in the art would not have been motivated to make a Blimp transgenic animal in order to specifically identify and isolate ASCs, or at least very least, would not have reasonably expected the successful results achieved by the invention.

With respect to the remaining claims, namely, claim 1 and its dependent claims (directed to a genetically modified non-human organism), claim 50 and its dependent claims (directed to an isolated genetically modified cell), as well as claims 61 and 67 and their dependent claims (directed to methods for screening for agonists or antagonists of differentiation to antibody secreting cells, *in vitro* and *in vivo*), the genetically modified organism and cells are further defined to be capable of producing functional Blimp protein. This feature further distinguishes the claimed subject matter from the teaching of Glimcher.

Specifically, Glimcher alleges that XBP-1 is a regulator of plasma cell differentiation

and T cell subset activity; and therefore the transgenic animal, cells and related screening assays disclosed by Glimcher rely on the presence of absence of the activity of the XBP-1 ***protein***, in contrast to the present invention where the transgenic organisms, cells and screening assays are based on the expression of the genetically modified *Blimp* ***allele***.

More specifically, in one aspect of the Glimcher disclosure, the assays of screening for antagonist or agonist compounds of plasma cell differentiation employ an indicator composition comprising XBP-1 protein. In this aspect, a compound of interest is selected based on the ability of the compound to modulate the activity of XBP-1 protein. See [0046]-[0052] of Glimcher. In this context, Glimcher teaches using a reporter gene and linking the reporter gene to an XBP-1 responsive regulatory element. See [0054]-[0061]. This aspect of Glimcher's disclosure does not teach or suggest placing a reporter gene into an allele of the endogenous *Blimp* gene (in fact, Glimcher suggests XBP-1 to act downstream of Blimp in [0214]). In addition, contrasting to the present invention where the screening assays are based on the ***expression*** of the genetically modified *Blimp* ***allele***, the Glimcher's assay design relies on the ***activity*** of XBP-1 ***protein***.

In the other aspect of the Glimcher disclosure, the assays of screening for antagonist or agonist compounds of plasma cell differentiation employ cells that are "XBP-deficient", which can be obtained from an XBP-deficient transgenic animal. See, e.g., [0082]-[0083] of Glimcher. To the contrary, the transgenic organism and cells recited in claims 1, 50, 61 and 67 are capable of producing functional Blimp protein.

Therefore, apart from the notion that one would not have been motivated to substitute XBP-1 of Glimcher with Blimp because those skilled in the art would not have considered Blimp and XBP-1 as equivalent markers, even if one were to attempt to follow the teachings of

Glimcher, one would not have arrived at the presently claimed genetically modified organisms, cells or screening assays.

The deficiencies of Glimcher, and the other cited references taken in combination, result from a failure of Glimcher and the other cited references to recognize that the expression from the *Blimp* gene coincides with the commitment to differentiate to ASCs or the identity of ASCs themselves. This recognition is uniquely provided by the present invention.

Accordingly, Applicants respectfully submit that the claims, as presented herein, are not obvious over Glimcher et al. in view of Shaffer et al., Pol et al., and Mountford et al. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Respectfully submitted,

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